HFA305

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 23 2003

03P-0121/CP1 0269 '03 SEP 24 P1:28

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Washington, DC 20001

Re: Docket No. 03P-0121/CP1

Dear Messrs. Dubeck and Stearns:

I am writing to inform you that the Food and Drug Administration (FDA) has not yet resolved the issues raised in your citizen petition received on March 26, 2003. Your petition requests that FDA require filers of abbreviated new drug applications (ANDAs) containing paragraph IV certifications to include in all ANDA amendments one of two possible certifications. The required certification would be either that (1) the ANDA filer will provide to the NDA holder and patent owner a new notice of patent certification, or (2) if the amendment does not involve any changes to the chemistry, manufacturing, and controls (CMC) section of the ANDA, the filer will notify the NDA holder and patent owner to that effect.

FDA has been unable to reach a decision on your petition because it raises significant issues that require additional review and analysis by the Agency. This interim response is provided in accordance with FDA regulations on citizen petitions (21 CFR 10.30(e)(2)). We will respond to your petition as soon as we have reached a decision on your request.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

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March 26, 2003

Via Hand Delivery

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
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CITIZEN PETITION

On behalf of Biovail Corporation, the undersigned submits this petition under 21 C.F.R. § 10.30 and section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDC Act) requesting that the Commissioner of Food and Drugs enforce the patent certification requirements in the FDC Act to curb abuses by the sponsors of Abbreviated New Drug Applications (ANDAs).

A. Action Requested

Biovail requests that the Commissioner of the Food and Drug Administration (FDA) enforce the existing regulation that requires an ANDA applicant that has not yet received final approval, to make a new patent certification under 21 C.F.R. §§ 314.94(a)(12)(i) and 314.94(a)(12)(viii)(C)(1) whenever the patent certification is no longer "accurate" as occurs when a Paragraph IV certification has been made and amendments to the ANDA alter the characteristics of the generic drug. FDA should require all Paragraph IV ANDA filers to include in all ANDA amendments a certification that it will provide to the NDA holder and patent owner (1) a new notice of patent certification or (2) if the amendment does not involve any changes to the chemistry, manufacturing, and controls (CMC) section of the ANDA, a notification to that effect. Requiring a new patent certification whenever the CMC portion of an ANDA is amended will allow a pioneer drug company to ensure that any new patent infringement issues are promptly addressed.

This action is needed to account for changes in the regulatory process for ANDA approvals. The Agency's original regulations were promulgated in final form on October 3, 1994 (59 *Fed. Reg.* 50338), reflecting interpretations and policy decisions that had been in place for some time. Throughout this time, FDA's regulations have provided that "an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate." 21 C.F.R. § 314.94(a)(12)(viii)(C)(1). Since the "certification" and "notice of patent certification" are inextricably tied together in the regulatory scheme, it is reasonable to conclude that any relevant

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changes in the factual and legal bases presented in the notice of certification cause the certification itself to no longer be accurate. An ANDA amendment that changes the process by which a drug is manufactured may affect patent infringement issues independent of its effect on the approvability of the ANDA.

As a result of developments since mid-1998, however, those interpretations (and the policy assumptions that supported them) have been superceded. The Agency's patent certification requirements must be more rigorously enforced to ensure that the drug product that is ultimately approved under an ANDA is the same product that has been the subject of the patent certification(s).

B. Statement of Grounds

1. The Regulatory Ground Rules Have Changed Dramatically

The ANDA approval landscape has changed dramatically since FDA first promulgated its regulations implementing The Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act"). In its original final regulations governing patent and exclusivity issues for ANDAs, FDA's "successful defense" requirement ensured that all ANDAs were reviewed on their own merits, and the benefit of the 180-day exclusivity period[1] went only to a deserving ANDA applicant.[2] This regulation, and its effect on determining which ANDA applicant would receive 180-day exclusivity, were successfully challenged in two cases in April 1998.[3] Following those decisions, FDA changed its interpretation of the statute and put industry on notice of its new position in a guidance document, concluding that the first applicant to submit an ANDA with a Paragraph IV certification will be eligible for 180-day exclusivity even if it is not sued for patent infringement.[4] FDA then modified its regulations to account for these

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1 FDC Act § 505(j)(5)(B)(iv).

2 "If an [ANDA] contains a [Paragraph IV certification] and the application is for a generic copy of the same listed drug for which one or more substantially complete [ANDAs] were previously submitted containing a [Paragraph IV certification] and the applicant submitting the first application has successfully defended against a suit for patent infringement brought within 45 days" of the required patent notice, the first applicant would receive the 180-day exclusivity. 21 C.F.R. § 314.107(c)(1) (1997) (emphasis added) (regulation now superceded).

3 *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060 (D.C. Cir. 1998); *Granutec, Inc. v. Shalala*, 46 U.S.P.Q.2d 1398, 1998 WL 153410 (4th Cir. (N.C.)) (unpublished disposition).

judicial developments. 63 *Fed. Reg.* 59712 (Nov. 5, 1998). As part of this evolving landscape, FDA has been forced to broaden its definitions of "court"[5] and "decision"[6] for purposes of certain statutory triggers.

The result of this turmoil is a regulatory environment for ANDA applicants where the emphasis is now simply on being the first to file an application. There is no longer an incentive to be the first to file the ANDA with the strongest data or the first to file the ANDA with the technology least likely to infringe the pioneer's patents. This new-found emphasis on timing over quality opens the door for ANDA applicants to "submit first and fix later."

2. The New Regulatory Environment Warrants Close FDA Scrutiny of Amendments Made During the ANDA Review Process

FDA should be particularly wary of any changes made to the formulation, specifications, or manufacturing procedures of a product while the ANDA is still under review. In the context of considering an ANDA applicant's entitlement to 180-day generic drug exclusivity, FDA has expressed great concern about these types of changes. For example, the Agency had, at one time, proposed that "if the applicant must conduct a new bioequivalence study to obtain approval of the ANDA, the application will not be considered to be substantially complete and the applicant will not be eligible for exclusivity." 64 *Fed. Reg.* 42873, 42875 (August 6, 1999) (column 2).[7] Similarly, FDA felt that "if the first applicant submits a new paragraph IV certification because, for example, it makes a formulation change requiring a supplement or an amendment to its ANDA, it may no longer be accorded first applicant status." *Id.* (column 3) (emphasis added).

Changes to the formulation, specifications, or manufacturing procedures of a product subject to an ANDA should be particularly suspect after a tentative approval letter has been

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[4] FDA, "Guidance for Industry - 180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act" (June 1998). The "no lawsuit required" interpretation was upheld in *Purepac Pharmaceutical Co. v. Friedman*, 162 F.3d 1201 (D.C. Cir. 1998).

[5] *Mylan Pharmaceuticals, Inc. v. Shalala*, 81 F.Supp.2d 30, 47 (D.D.C. 2000); 65 *Fed. Reg.* 43233 (July 13, 2000) (revising 21 C.F.R. §314.107(e)).

[6] *Teva Pharmaceuticals, USA. Inc. v. FDA*, 182 F.3d 1003 (D.D.C. 1999).

[7] FDA has withdrawn this proposed rule, entitled "180-Day Generic Drug Exclusivity for Abbreviated New Drug Applications." *See* 67 *Fed. Reg.* 65593 (November 1, 2002). Nevertheless, the principles discussed are still relevant to the approval of ANDAs.

issued. As FDA describes the significance of a tentative approval letter, an ANDA would have been approved, but for a delay required by existing patent or exclusivity requirements.[8] As a result, any change in these characteristics should be treated with considerable suspicion. One option for handling these changes would be to consider any such submission following a tentative approval letter to constitute a "major" amendment to the ANDA, thereby discouraging companies from planning a "submit first and fix later" strategy and ensuring the Agency has sufficient time to thoroughly investigate the basis for the change and confirm that it is not due to some underlying fundamental problem with the application. Due to the confidential nature of the drug review process, examples of situations where significant changes are made following the tentative approval decision are not publicly known. Biovail believes FDA is aware of situations where important changes have been made to ANDAs following tentative approval.

FDA's latest regulatory initiative in this area is the publication of a proposed rule intended to, among other provisions, re-interpret the FDC Act to permit only one 30-month delay in the approval of an ANDA. 67 *Fed. Reg.* 65448 (October 24, 2002). Whatever the merits of the proposal, it does not address the issue of concern in this petition. Indeed, a large trade association of the pharmaceutical industry specifically identified this shortcoming in its comments to FDA on the proposal.[9] Thus, even FDA's on-going rulemaking proceedings do not appear likely to address the potential problems created by a change in the formulation of an ANDA.

3. Amendments Can Affect the Accuracy of Patent Certifications

FDA's regulations provide that "an applicant shall amend a submitted [patent] certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate." 21 C.F.R. § 314.94(a)(12)(viii)(C)(1). Amendments to a pending ANDA can mean that the proposed drug product has changed in important respects from the product described in the original ANDA, and these changes may have significant patent infringement implications. Since such changes may affect the course of the patent infringement litigation, prompt disclosure is essential to resolving any question about the accuracy of the patent certification and the factual/legal justifications presented in the notice of certification. The fact that an original ANDA contained a Paragraph IV certification and, after amendment, the appropriate certification is still a Paragraph IV

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[8] "The only difference between a full approval and a tentative approval is that the final approval of these applications is delayed due to existing patent or exclusivity on the innovator's drug product." Food and Drug Administration. *CDER 2000 Report to the Nation: Improving Public Health Through Human Drugs.* Rockville, Maryland, 2001 (page 13) (document available from FDA at: http://www.fda.gov/cder/reports/RTN2000/RTN2000.HTM).

[9] *See* Comments of the Pharmaceutical Research and Manufacturers of America (PhRMA), Docket 02N-0417/C27 (dated December 23, 2002), pages 9 – 10.

certification is inadequate to conclude that the certification is still "accurate." As discussed in more detail below, under 35 U.S.C. § 271(e)(2), the jurisdiction of a court to adjudicate a potential patent infringement is critically dependent upon the identity and characteristics of the drug product that is the subject of the ANDA. Any amendment of the CMC section of the ANDA redefines the product that is covered by the application and, at the very least, requires a fresh assessment of whether infringement has arisen.

Biovail is well aware of FDA's unwillingness to involve itself in evaluating substantive patent matters because of the Agency's professed lack of expertise in this area.[10] This Petition does not request or require that FDA venture into these turbulent waters. However, FDA must implement the patent certification procedures in a way that affords a pioneer drug company the opportunity to protect its intellectual property prior to the approval of an ANDA. This process is part of the carefully balanced compromise between maintaining patent protection and simplifying the generic drug approval process reached in Hatch-Waxman Act. FDA's current "hands off" approach to patent matters is an abdication of the Agency's responsibility to ensure that ANDAs are in compliance with 21 C.F.R. § 314.94(a)(12)(viii)(C)(1) prior to approval.

When an ANDA is submitted originally and the applicant seeks approval before the expiration of any patents listed in the *Orange Book*, the applicant must make a certification "that such patent [on the innovator drug product] is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the [ANDA] is submitted."[11] The product that ultimately will be approved under the ANDA will reflect any modifications made through amendments to the ANDA prior to approval. This product may differ in important respects from the product that was originally described in the ANDA.

The courts have held that the patent infringement inquiry "'is properly grounded in the ANDA application and the extensive materials typically submitted in its support.' Therefore, it is proper for the court to consider the ANDA itself, materials submitted by the ANDA applicant in support of the ANDA, and any other relevant evidence submitted by the applicant or patent holder."[12] Indeed, "the question of infringement must focus on what the ANDA applicant will likely market if its application is approved . . .."[13]

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10 FDA reports that it "does not have the expertise or the desire to become involved in issues concerning patent law and sufficiency of notice." 59 *Fed. Reg.* at 50350 (FDA response to comment 60).

11 FDC Act § 505(j)(2)(A)(vii)(IV) (emphasis added); 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

12 *Bayer v. Elan Pharmaceutical Research Corp.*, 212 F.3d 1241, 1248 - 49 (Fed.Cir. 2000) (internal citation omitted).

13 *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed.Cir. 1997).

Biovail is not asking FDA to consider substantive patent issues as part of its ANDA review. Rather, the point is that the product an ANDA applicant expects to have approved (following numerous amendments and other changes) may not be the product described in its original ANDA and that was the subject of a patent certification given many months (if not years) earlier. In that case, the applicant's patent certification would no longer be "accurate" because the notification provided in connection with this certification would no longer be relevant to the product the applicant intends to market. A new certification must be required before the ANDA can be approved.

This problem can be remedied by granting the requested action, with little additional work on FDA's part. FDA should require all Paragraph IV ANDA filers to include in all ANDA amendments a certification that it will provide to the NDA holder and patent owner (1) a new notice of patent certification or (2) a notification that the amendment does not involve any changes to the CMC section of the ANDA. This process will not involve FDA in any substantive patent disputes. Rather, the Agency's only responsibility would be to ensure that the ANDA applicant has provided an appropriate notification for each amendment to the ANDA. FDA already performs this documentation function for patent certifications made for the original ANDA submission, and it is consistent with the Agency's "ministerial" role in patent listing matters.[14] The notice concerning subsequent amendments to the ANDA would provide the innovator company with the opportunity to seek a judicial determination of whether the changes to the ANDA are such that the drug "for which the applicant is seeking approval" would infringe the listed patent(s).

4. Mandatory Reissuance of Paragraph IV Certifications for All CMC Amendments Will Not Create New Abuses

The purpose of this petition is not to create extra-statutory obstacles to the approval of generic drug products. Rather, it is to ensure that the statutory provisions of the Hatch-Waxman amendments to the FDC Act are faithfully followed. The CMC section of virtually every ANDA is amended to some extent during the FDA approval process. In theory, this could mean that the statutory 30 month delay would run not from the date of the initial notification, but from the date of the notification that accompanied submission of the last CMC amendment. This would effectively extend the 30 month stay in a manner not intended by Congress. Fortunately, Congress had the foresight to include a provision which prevents that outcome. Section 505(j)(5)(B)(iii) of the FDC Act provides that the court which is adjudicating an alleged

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[14] "FDA has . . . reiterat[ed] . . . that its role in listing patents is 'purely ministerial' and that it 'does not have the expertise nor the resources to resolve complex patent coverage issues.'" *Mylan Pharmaceuticals, Inc., v. Thompson*, 139 F.Supp.2d 1, 11 (D.D.C. 2001) (internal citations omitted).

infringement under 35 U.S.C. § 271(e)(2) which gives rise to the 30 month delay of FDA approval when such action is timely commenced may order that the delay of FDA approval be "shorter or longer ... because either party to the action failed to reasonably cooperate in expediting the action...."

If an amendment to the CMC section of a pending ANDA alters the nature and/or manner by which an alleged infringement arises and/or makes proof of infringement more complicated or difficult to prove, the plaintiff would be entitled to either of two remedies. It can point to the delays created by the amendment and seek to have the original 30 month delay appropriately extended, or it could initiate a new suit within 45 days of receiving the new notification and, thereby, trigger a new 30 month delay. If the plaintiff were to seek to delay FDA approval by either of these means in a situation where the CMC amendment had absolutely no impact on the infringement issues that were in dispute, such actions would easily constitute failure to reasonably cooperate in expediting the action and an extension of the 30 month delay would not be granted or the new 30 month period that would arise by statutory action if a new suit were timely filed could be appropriately shortened.

One last possible scenario bears mention. A patent holder might choose to not file an infringement suit when initially notified and gamble that a subsequent notification triggered by an amendment to the CMC section of the ANDA would be required prior to approval. Again, we would expect that the court would have no difficulty appropriately adjusting the 30 month period that would arise if a reasonable basis existed for the infringement action to be initiated at the time of the initial (or any earlier) notification. In other words, if the amendment, *per se*, did not create a new potential for infringement, the failure to have brought the infringement action sooner would be a clear failure by the patent holder to reasonably cooperate in expediting the action and the court would order whatever curtailment or elimination of the 30 month delay it deemed appropriate.

Automatic updating of Paragraph IV certifications for all CMC amendments ensures that the courts are entertaining only those actions under 35 U.S.C. § 271(e) that relate to products ANDA applicants intend to market. The court has ample authority in dealing with new actions filed in response to these amendment-triggered certifications to put an end to the current ability of ANDA filers to hide behind CMC amendments to gain approval of a drug product that may be more likely to be found to be infringing than the drug product described in the original ANDA, without exposing the infringing product to litigation under 35 U.S.C. § 271(e)(2). The court also has ample authority to thwart any attempt by patent owners to utilize the additional notifications to improperly extend the default 30 month delay that arises from the timely filing of an infringement suit after receipt of a patent notification. Where the amendment does alter the basis for infringement, appropriate extensions of the 30 month period would be ordered.

5. Conclusion

For the reasons presented above, Biovail requests that the Commissioner adopt the patent certification requirements described in Part A of this Citizen Petition.

C. Environmental Impact

Biovail claims a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

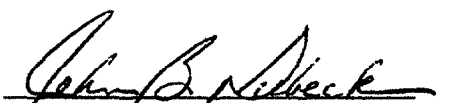
D. Economic impact

This information will be provided upon request of the Commissioner.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



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